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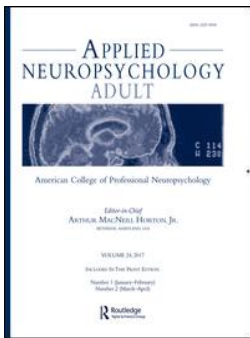
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Effects of methylphenidate on memory functions of adults with ADHD

Anselm B. M. Fuermaier^a, Lara Tucha^a, Janneke Koerts^a, Matthias Weisbrod^{b,c}, Klaus W. Lange^d, Steffen Aschenbrenner^e and Oliver Tucha^a

^aDepartment of Clinical and Developmental Neuropsychology, University of Groningen, Groningen, The Netherlands; ^bDepartment of Psychiatry and Psychotherapy, SRH Clinic Karlsbad-Langensteinbach, Karlsbad-Langensteinbach, Germany; ^cSection for Experimental Psychopathology, Centre for Psychosocial Medicine, University of Heidelberg, Heidelberg, Germany; ^dDepartment of Experimental Psychology, University of Regensburg, Regensburg, Germany; ^eDepartment of Clinical Psychology and Neuropsychology, SRH Clinic Karlsbad-Langensteinbach, Karlsbad-Langensteinbach, Germany

ABSTRACT

Neuropsychological research on adults with attention deficit hyperactivity disorder (ADHD) revealed considerable impairments in memory functions related to executive control. However, only limited evidence exists supporting the effects of pharmacological treatment using methylphenidate (MPH) on memory functions. The aim of the present study was, therefore, to explore the impact of MPH on various memory functions of adults with ADHD. Thirty-one adults with ADHD treated with MPH, 36 adults with ADHD not-treated with MPH, and 36 healthy individuals were assessed on several aspects of memory, including short-term memory, working memory, retrospective memory, prospective memory, and source memory. Multivariate statistical analyses were applied to compare memory functions between groups. Nonmedicated adults with ADHD showed considerable impairments in memory functions related to executive control. Adults with ADHD treated with MPH showed improved memory functions when compared to nonmedicated patients, but were still impaired when compared to healthy controls. The present study emphasized the severity of memory impairments of adults with ADHD. A pharmacological treatment with MPH appeared to improve memory, but does not normalize functioning. Additional treatment intervention (e.g., cognitive-behavioral therapy) is therefore necessary.



KEYWORDS

Adult ADHD; cognition; memory; methylphenidate; treatment

ADHD in adulthood is strongly associated with academic and occupational failure, social dysfunction, low self-esteem, and reduced quality of life (Agarwal, Goldenberg, Perry, & IsHak, 2012; Biederman, 2005; Canu & Carlson, 2007; Canu, Newman, Morrow, & Pope, 2008; Mueller, Fuermaier, Koerts, & Tucha, 2012). A clinical evaluation of symptoms and impairments of patients with ADHD benefits from an objective assessment of neuropsychological functions using standardized psychometric tests. Most theories on neuropsychological functions of adults with ADHD proposed a primary deficit of inhibitory executive functions (Barkley, 1997; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Tannock, 1998) which resulted in a large body of research examining various functions associated with executive control, including focused attention, divided attention, vigilance, working memory, inhibition, set-shifting, verbal fluency, and problem solving (Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2010; Boonstra, Oosterlaan,

Sergeant, & Buitelaar, 2005; Dinn, Robbins, & Harris, 2011; Fuermaier et al., 2015; Herve, Epstein, & Curry, 2004; Lange et al., 2014; Schoechlin & Engel, 2005; O. Tucha et al., 2005, L. Tucha et al., 2008, 2009).

More recently, theoretical considerations and empirical research suggested that executive dysfunctions of adults with ADHD might also adversely affect memory functions of patients (Altgassen, Koch, & Kliegel, 2014; Altgassen, Kretschmer, & Kliegel, 2014; Fuermaier, Tucha, Koerts, Aschenbrenner, Weisbrod, et al., 2013; Fuermaier et al., 2014, 2015; Fuermaier, Tucha, Koerts, Aschenbrenner, Westermann, et al., 2013; Muir-Broadbent, Rosenstein, Medina, & Soderberg, 2002; Pollak, Kahana-Vax, & Hoofien, 2008; Seidman, Biederman, Weber, Hatch, & Faraone, 1998). For example, adults with ADHD have been shown to suffer from deficits of both the encoding of new information as well as the recall of stored information, whereas the retention of learned information

CONTACT Anselm B.M. Fuermaier  a.b.m.fuermaier@rug.nl  Faculty of Behavioral and Social Sciences, Department of Clinical and Developmental Neuropsychology, University of Groningen, Grote Kruisstraat 2/1, Groningen 9712 TS, The Netherlands.

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was found to be unimpaired (forgetting rate comparable to normal functioning level; Fuermaier, Tucha, Koerts, Aschenbrenner, Weisbrod, et al., 2013; Kaplan, Dewey, Crawford, & Fisher, 1998; Muir-Broaddus et al., 2002; Pollak et al., 2008; Seidman et al., 1998). Efficient encoding and recall processes (i.e., free recall) were both attributed to intact executive functions, including semantic clustering, effortful rehearsal, strategic use of mnemonics, and careful consideration of response alternatives (Pollak et al., 2008). Retention of learned information, however, does not primarily depend on these cognitive processes. Furthermore, adults with ADHD were demonstrated to have deficits in source memory (Fuermaier, Tucha, Koerts, Aschenbrenner, Weisbrod, et al., 2013; White & Marks, 2004) and prospective memory (Altgassen, Koch, et al., 2014; Altgassen, Kretschmer, et al., 2014; Fuermaier, Tucha, Koerts, Aschenbrenner, Westermann, et al., 2013), two memory components which were stressed to require high demands on executive control (Glisky, Polster, & Routhieaux, 1995; Kliegel, McDaniel, & Einstein, 2000). Source memory comprises information *where* and *when* an event took place and *how* it was acquired, causing biographic events to become vivid and rich (Drag, Bieliauskas, Kaszniak, Bohnen, & Glisky, 2009). Prospective memory can be defined as the performance of an intended action at a particular point in the future, such as taking prescribed medication or keeping an appointment. Prospective memory was stressed by several authors to be an essential cognitive ability for successful social and occupational functioning (Crovitz & Daniel, 1984; Kliegel & Martin, 2003; Terry, 1988).

The impairments of cognition associated with ADHD emphasize the need for an effective treatment. First-line choice of treatment is often a pharmacological treatment using stimulants, that is, methylphenidate (MPH; Vidal-Estrada, Bosch-Munso, Nogueira-Morais, Casas-Brugue, & Ramos-Quiroga, 2012; S. B. Wigal, 2009; T. Wigal et al., 1999). A large number of studies on adults with ADHD reported positive effects of MPH on several aspects of cognition, including alertness, vigilance, selective attention, divided attention, working memory, response inhibition, and flexibility (Aron, Dowson, Sahakian, & Robbins, 2003; Coghill et al., 2013; O. Tucha, Mecklinger et al., 2006; L. Tucha et al., 2011; Turner, Blackwell, Dowson, McLean, & Sahakian, 2005). However, considerably less evidence exists presenting the effects of MPH on memory functions of adults with ADHD. For example, there are only two studies available showing that MPH significantly improves free recall of learned information of adults with ADHD (Riordan et al., 1999; Verster et al.,

2010). The effect of MPH on other aspects of memory of adults with ADHD, such as prospective memory or source memory, is still unknown. In this respect, it might be of interest that numerous studies did not only demonstrate that children and adolescents with ADHD also display deficits in the above mentioned memory functions (e.g., Gau & Shang, 2010; Kataria, Hall, Wong, & Keys, 1992; Kerns & Price, 2001; Kingdon, Cardoso, & McGrath, 2015; Kliegel, Ropeter, & Mackinlay, 2006; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Muir-Broaddus et al., 2002; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005) but also that stimulant drug treatment has the potential to improve these functions considerably (e.g., Bedard, Martinussen, Ickowicz, & Tannock, 2004; Mehta, Goodyer, & Sahakian, 2004; Rhodes, Coghill, & Matthews, 2005; Vance, Maruff, & Barnett, 2003). Furthermore, a recent review examining the impact of MPH on different domains of cognition of healthy individuals revealed that single doses of MPH enhance aspects of memory functioning (Linszen, Sambeth, Vuurman, & Riedel, 2013). While about two thirds of studies examining working memory and about one third of studies examining verbal learning and memory observed significant improvements following MPH intake, visual learning and memory has been found to be unaffected by single doses of MPH.

The aim of the present study was, therefore, to examine the effect of MPH on memory functioning of adults with ADHD. A comprehensive assessment of several aspects of memory was performed on three groups of participants, that is, adults with ADHD treated with MPH, adults with ADHD not-treated with MPH, and healthy individuals. A basic test battery of attention was also administered to all participants in order to describe their level of cognition on routine neuropsychological measures used for adults with ADHD. Given theoretical models describing ADHD as disorder of executive control (Barkley, 1997; Castellanos et al., 2006), and based on previous research revealing memory impairments in adults with ADHD (e.g., Altgassen, Koch, et al., 2014; Fuermaier, Tucha, Koerts, Aschenbrenner, Weisbrod, et al., 2013; Fuermaier, Tucha, Koerts, Aschenbrenner, Westermann, et al., 2013; Pollak et al., 2008; Seidman et al., 1998), it was expected that (a) adults with ADHD not-treated with MPH showed impaired memory functions when compared to healthy individuals, with the largest effect sizes expected in memory functions which required high demands on executive control, i.e., free recall of information (compared to word recognition), source memory and prospective memory. Furthermore, given the conclusive findings demonstrating that MPH effectively improves symptoms, cognition and functioning of

adults with ADHD (e.g., Coghill et al., 2013; Vidal-Estrada et al., 2012; S. B. Wigal, 2009), it was hypothesized that (b) adults with ADHD treated with MPH showed improved memory performance compared to patients not-treated with MPH. However, considering that MPH has been shown to improve cognition of adults with ADHD but did not normalize their level of performance (O. Tucha, Mecklinger et al., 2006, L. Tucha et al., 2011), it was expected that also adults with ADHD treated with MPH showed impaired memory functions when compared to healthy individuals. To the best of our knowledge, the present study was the first to explore the impact of stimulant drug treatments on various aspects of memory of adults with ADHD. The study has relevance and important implications for both research and clinical practice.

Methods

Participants

Three groups of participants were recruited, that is, a group of adults with ADHD not-treated with MPH, a group of adults with ADHD treated with MPH and a group of healthy individuals.

Patients with ADHD

Patients were self-referred or referred from local psychiatrists or neurologists to the Department of Psychiatry and Psychotherapy, SRH Group, Karlsbad-Langensteinbach, Germany. A diagnostic assessment for ADHD in adulthood as well as a participation in the research project was offered to all participants. Diagnostic assessments were performed by experienced clinicians and involved a clinical psychiatric interview according to DSM-IV criteria for ADHD as devised by Barkley and Murphy (1998) including the retrospective assessment of symptoms in childhood and current symptoms. Moreover, all participants completed two standardized self-report rating scales designed to quantify ADHD symptoms currently and retrospectively (Rösler, Retz-Junginger, Retz, & Stieglitz, 2008). Childhood ADHD symptoms were self-rated with the short version of the Wender Utah Rating Scale (WURS-K) including 25 items on a five-point scale (Ward, Wender, & Reimherr, 1993). Severity of ADHD symptoms in adulthood was self-rated with the ADHD Self-Report Scale consisting of 18 items on a four-point scale corresponding to the diagnostic criteria of DSM-IV (American Psychiatric Association, 1994; Rösler et al., 2008). When participants were asked to rate current symptom severity, patients with ADHD treated with MPH were

instructed to refer to typical situations when not being treated with MPH and to rate the severity of experienced ADHD symptoms in these situations. This approach was chosen to get an indication of self-reported symptom severity not affected by pharmacological treatment which can be compared between the two groups of patients (treated and not-treated with MPH). Intellectual functions of all participants were measured using the *Multiple Choice Vocabulary Test* (Lehrl, 1995). Patients were selected according to diagnosis, intellectual functions (IQ), and willingness to participate in the study. Potential patients were excluded (a) if they had clinically significant or chronic medical conditions (e.g., recent operations, cardiac failure, kidney disease or Crohn's disease), (b) if there was a history suggestive of 'psychosis' (indicating schizophrenia, delusional disorder, depressive disorder with psychotic features or manic episode), (c) if there was a history of neurological disorders including head injury, (d) if there was a history of substance abuse disorder during the previous two months, (e) if the initial psychiatric assessment indicated a current major depressive episode, or (f) if estimated premorbid verbal IQ was <85. In total, 67 adults with ADHD were recruited. Of the 67 adults with ADHD, 36 patients were not-treated with MPH and 31 patients were currently treated with MPH. Of the 36 adults with ADHD not-treated with MPH, 14 met DSM-IV criteria for ADHD – predominantly inattentive type (ADHD-I), one patient met criteria for ADHD – hyperactive-impulsive type (ADHD-H), and 21 patients met criteria for ADHD – combined type (ADHD-C). Seven patients were diagnosed with comorbid psychiatric disorders, including mood disorders ($n=6$) and personality disorder ($n=1$). All 31 patients with ADHD treated with MPH received individual tailored and clinical appropriate doses of MPH with a mean dose of 35.5 mg per day and with individual doses ranging from 10 to 80 mg per day. All patients were treated with MPH regularly on a daily basis. Seven of these patients met DSM-IV criteria for ADHD – predominantly inattentive type (ADHD-I), one patient met criteria for ADHD – hyperactive-impulsive type (ADHD-H), and 23 patients met criteria for ADHD – combined type (ADHD-C). Fourteen exhibited one or more comorbidities, including mood disorders ($n=10$), personality disorders ($n=2$), anxiety disorders ($n=3$), somatoform disorders ($n=2$), obsessive-compulsive disorder ($n=1$), substance abuse in the past ($n=1$), and posttraumatic stress disorder ($n=1$). Furthermore, seven patients on MPH were also currently treated with antidepressant medication because of comorbid disorders.

Healthy individuals

Furthermore, 96 healthy individuals were assessed. Healthy individuals were recruited via public announcements, word-of-mouth and through contacts of the researchers involved. None of the healthy individuals reported to have a history of neurological or psychiatric diseases and none was taking any medication known to affect the central nervous system. All healthy individuals completed the same self-report questionnaires for current and retrospective ADHD symptoms prior to the assessment (Rösler et al., 2008). Intellectual functions of all participants were measured using the *Multiple Choice Vocabulary Test* (Lehrl, 1995). From the 96 healthy individuals, 36 individuals were selected according to age, sex and intellectual functions in order to obtain a group with characteristics which are comparable to the two patient groups. Characteristics of healthy individuals and patients with ADHD are presented in Table 1. Healthy individuals, adults with ADHD not-treated with MPH and adults with ADHD on MPH did not differ with regard to age ($F(2,100) = 0.004$; $p = .996$), gender ($\chi^2(2) = 2.94$; $p = .230$) and intellectual functions ($F(2,100) = 1.03$; $p = .362$). However, as expected, significant group differences were obtained with regard to the self-reported symptom severity of both current ADHD symptoms ($F(2,100) = 78.95$; $p < .001$) and retrospective ADHD symptoms ($F(2,100) = 124.55$; $p < .001$). Whereas the two patient groups did not differ in either current symptoms ($p = 0.278$) or retrospective symptoms ($p = 0.703$), healthy individuals showed significant lower symptom scores on the two scales ($p < .001$ for all comparisons).

Materials

Intellectual functions

Intellectual functions (IQ) were measured using the *Multiple Choice Vocabulary Test* (Lehrl, 1995). The *Multiple Choice Vocabulary Test* is a valid and short test procedure which provides a measure of intellectual functioning.

Alertness

Alertness was measured with a computerized test from the *Testbattery for Attentional Performance* (Zimmermann & Fimm, 2008). In this test, participants were asked to respond as quickly as possible to the presentation of a visual stimulus by pressing a specified button. The stimulus appeared on the screen either with or without prior warning, providing measures of tonic and phasic alertness (reaction times).

Selective attention

In the Visual Scanning test (Zimmermann & Fimm, 2008) a series of matrices was presented in the center of the computer screen. Participants were asked to press a response button as quickly as possible whenever a matrix contained a predefined critical stimulus or to press another response button if the critical stimulus was not contained. The reaction time for correct responses of trials which did not contain a critical stimulus was registered.

Vigilance

In the vigilance test (Zimmermann & Fimm, 2008), a sequence of tones was presented to the participant,

Table 1. Characteristics of healthy individuals, adults with ADHD not-treated with MPH (ADHD Off-MPH), and adults with ADHD treated with MPH (ADHD On-MPH).

	Healthy individuals		Adults with ADHD			
	<i>M</i> ± <i>SD</i>	% with impairment ^g	Off-MPH		On-MPH	
			<i>M</i> ± <i>SD</i>	% with impairment ^g	<i>M</i> ± <i>SD</i>	% with impairment ^g
<i>n</i>		36		36		31
Descriptive variables						
Age (in years)	34.1 ± 10.5		34.1 ± 10.9		33.9 ± 9.6	
Gender (female/male)	20/16		21/15		12/19	
Intellectual functions (IQ) ^a	102.9 ± 8.2		102.2 ± 13.0		105.9 ± 12.3	
Comorbidity ^b	–		7 (6/1/0/0/0/0/0)		14 (10/2/3/2/1/1/1)	
Self-reported ADHD symptom severity						
Childhood symptoms (WURS-K) ^c	10.8 ± 7.9		43.7 ± 11.6 ^d		45.8 ± 11.5 ^d	
Current symptoms (ASR) ^e	9.3 ± 4.2		32.2 ± 8.8 ^d		28.9 ± 11.0 ^{d,f}	
Standard measures of cognition						
Alertness – tonic (in msec)	243.0 ± 39.4	8.3	279.9 ± 59.6 ^d	25.0	249.0 ± 37.6 ^h	6.5
Alertness – phasic (in msec)	240.5 ± 35.3	5.6	270.4 ± 60.6 ^d	13.9	243.4 ± 32.3 ^h	6.5
Selective attention (in sec)	4.53 ± 1.59	5.7	5.72 ± 1.53 ^d	25.7	5.04 ± 1.43	16.7
Vigilance (Omissions)	0.94 ± 1.29	5.6	2.75 ± 3.43 ^d	22.2	1.83 ± 3.09	12.9
Inhibition (Difference score)	26.6 ± 10.7	13.9	37.5 ± 17.9 ^d	22.2	29.5 ± 15.7	16.1

^aMultiple Choice Vocabulary Test (MWT-B); ^bNumber of patients affected with psychiatric comorbid disorders (some patients affected with more than one): mood disorders/personality disorders/anxiety disorders/somatoform disorders/obsessive-compulsive disorder/substance abuse in the past/posttraumatic stress disorder; ^cWender Utah Rating Scale – short version; ^d $p < .05$ when compared to healthy individuals; ^eADHD Self-Report Scale; ^fPatients with ADHD treated with MPH were instructed to refer to typical situations when not being treated with MPH and to rate the severity of experienced ADHD symptoms in these situations; ^gImpaired on a specific test if scored within the lowest 10% of scores of control participants ($n = 96$); ^h $p < .05$ when compared to adults with ADHD Off-MPH.

whereas two different types of tones could be distinguished, one with a high pitch and the other with a low pitch. The two types of tones were presented alternately in a constant rhythm. A target event was defined if two tones of the same pitch were directly presented after each other. The participant was requested to press a specified response button as quickly as possible if a target event occurred. The total duration of the vigilance test was 30 minutes. The number of omissions was registered as a measure of vigilance.

Inhibition

Inhibition was measured with the *Stroop Color-Word Interference test* (Bäumler, 1985; Stroop, 1935) which consisted of three conditions. In the *Color Word* condition, color words (YELLOW, GREEN, BLUE, and RED) printed in black ink were presented on a card and participants were required to read them as fast as possible. In the *Color Block* condition, colored rectangles (rectangles printed in yellow, green, blue, and red) were presented on a card and participants were required to name the color of the rectangles as fast as possible. In the *Color-Word Interference* condition, color words (YELLOW, GREEN, BLUE, and RED) were presented and printed in mismatching ink (e.g., RED printed in blue ink). The participants were required to state the color of the ink as fast as possible and to ignore the meaning of the printed word. The time in seconds to complete each trial was registered. As dependent variable, a difference score was calculated by subtracting the time needed for completion of the *Color Block* condition from the *Color-Word Interference* condition (Boonstra et al., 2005).

Short-term memory

The *Digit Span Forward* of the Wechsler Memory Scale (Wechsler, 1987) was applied as a measure of short-term memory. Series of numbers were read to the participants who were required to repeat the digits in the same order as presented. Subsequent series of numbers increased in length. The total number of correctly repeated sequences was registered.

Working memory

The *Digit Span Backward* (Wechsler, 1987) was performed to measure working memory. Series of numbers were read to the participants who were required to repeat the digits in reversed order. Subsequent series of numbers increased in length. The total number of correctly repeated sequences was registered.

Immediate and delayed story recall

Immediate and delayed story recall was assessed with the *Logical Memory I and II* (Wechsler, 1987). Two

short stories were read out to the participants by the experimenter. Participants were required to listen to the stories and to recall immediately and after a delay of about 20 minutes as many details as possible. The number of correctly recalled details was registered for the immediate and delayed story recall.

Immediate word recognition

A word list paradigm was used in order to test immediate word recognition (Fuermaier, Tucha, Koerts, Aschenbrenner, Weisbrod, et al., 2013). In the study phase of the immediate word recognition test, 40 unrelated nouns were presented consecutively for four seconds in the center of a computer screen. Participants were instructed to focus on the stimulus presentation and to use whatever mnemonics they thought were effective to memorize the words presented on the screen. A recognition test was performed immediately after the study phase. In the recognition test, all words from the study list as well as 40 additional words were presented consecutively in random order. The participants were instructed to indicate by pressing one of two predefined buttons whether the displayed word has been presented in the study phase or not. The number of correctly classified words was registered.

Delayed word recognition and retention

A word list paradigm was applied in order to test delayed word recognition (Fuermaier, Tucha, Koerts, Aschenbrenner, Weisbrod, et al., 2013). In the study phase of the delayed word recognition test, 40 unrelated nouns were again presented consecutively for four seconds. Participants were instructed to focus on the stimulus presentation and to use whatever mnemonics they thought were effective. A delay of 40 minutes followed the study phase. After the delay, a recognition test was performed and all words from the study phase and the distractor list which have not been presented before were presented consecutively in random order. The participants were instructed to indicate by pressing one of two predefined buttons whether the displayed word has been presented in the study phase or not. The number of correctly classified words was registered for the measure of delayed word recognition. Moreover, a measure of retention was obtained by calculating the quotient of the number of correctly classified words in the delayed word recognition test divided by the number of correctly classified words in the immediate word recognition test (as discussed previously).

Source memory

A source discrimination paradigm was applied to examine performance in source memory (Fuermaier,

Tucha, Koerts, Aschenbrenner, Weisbrod, et al., 2013). Twenty-eight unrelated German nouns were presented consecutively on a screen. Half of the words were displayed in blue font on the left hand side of a screen and the other half of the words were presented in green font on the right hand side. Each word appeared for seven seconds on the screen. The participants were instructed to focus on the stimulus presentation and to use whatever mnemonics they thought were effective to memorize the *words* AND the *corresponding source* of the words (blue font on the left side or green font on the right side). The source discrimination task was performed immediately after the study phase. All 28 words were presented in consecutive order, displayed in black font in the center of the screen. The participants were instructed to indicate *where/how* the word has been presented in the study phase, i.e., in blue font on the left side or in green font on the right side. The response was given by pressing one of two predefined buttons. The number of correctly classified words was registered.

Prospective memory

A planning task requiring delayed task execution was performed as a measure of prospective memory (Fuermaier, Tucha, Koerts, Aschenbrenner, Westermann, et al., 2013). In the present task, 10 subtests were introduced, grouped in five pairs of subtests, including arithmetic problems, cancellations tests, wording findings, screwing tests, and ball squeezing tests. Participants were asked to plan and, after a delay of about 60 minutes, to carry out these 10 subtests in a limited period of time under the consideration of certain rules. The rules of the present task included (a) a restriction in time (10 minutes), (b) a restriction in the sequence in which the subtests can be performed, (c) the possibility to perform two subtests simultaneously, and (d) the instruction to work on each of the 10 subtests at least once for a short period of time. In this task, several components of complex prospective memory can be distinguished, i.e., planning, recall, self-initiation, and execution. However, general task performance is indicated by a measure of switching between subtests (task switching). Task switching is calculated by the sum of actually initiated subtests at task execution under consideration of the rules. Task switching is crucial and may indicate general task performance since successful execution of the task requires active switching between subtests. Therefore, the number of initiated subtests at task execution was suggested as the primary measure for prospective memory (for details of the task performed, see Fuermaier, Tucha, Koerts, Aschenbrenner, Westermann, et al., 2013). However, considering that there is only one possibility to initiate the delayed

intention, it must be noted that the reliability of such single, one-time prospective memory tasks may be questionable.

Procedure

All participants were tested individually and received no reward for participation. Participants gave written informed consent at the beginning of the experiment. Subsequently, the neuropsychological assessment was performed, administered in two parts separated by a break to recover from possible fatigue. In the first part, tests for immediate word recognition, delayed word recognition and source memory were conducted. The order of the immediate word recognition test and the delayed word recognition test was counterbalanced across participants in order to control for learning and interference effects. The vigilance test was conducted between word list presentation and word recognition of the delayed word recognition test. After a short break, immediate and delayed story recall was performed to minimize interference with verbal learning tasks (i.e., word recognition test) of the first part of the assessment. Standard measures of cognition (i.e., tests for alertness, selective attention, and inhibition) were performed between immediate story recall and delayed story recall. All participants were debriefed at the end of the assessment. The total duration of the assessment was about two hours.

Ethics statement

The study was conducted in compliance with the Helsinki Declaration. Ethical approval was obtained by the ethics committee of the medical faculty of the University of Heidelberg, Germany.

Statistical analysis

Multivariate analyses of variance (MANOVA) were applied to compare cognitive functions of patients with ADHD treated with MPH, patients with ADHD not-treated with MPH and healthy individuals. MANOVA was performed twice in order to compare performance in attention and memory in separate analyses. The categorical variable of self-initiation in the prospective memory task was analyzed using chi-square test. Statistical significance of differences was calculated for each multivariate comparison (memory and attention) as well as for each dependent variable. Pairwise group comparisons were performed calculating Scheffé post-hoc analysis for each dependent variable. Furthermore, effect sizes (η^2 , Cohen's d) were calculated for all

comparisons. The index η^2 provides information about the proportion of variance which is accounted for by the factor group membership (three levels) in multivariate analyses. As described by Cohen (1988), η^2 is a function of the effect size index f . According to Cohen, a small effect size ($f = .10$) corresponds to an $\eta^2 = .0099$, a medium effect size ($f = .25$) to an $\eta^2 = .0588$ and a large effect size ($f = .40$) to an $\eta^2 = .1379$. The effect size d was computed for all pairwise comparisons of means. According to Cohen, negligible effects ($d < 0.20$), small effects ($0.20 \leq d < 0.50$), medium effects ($0.50 \leq d < 0.80$) and large effects ($d \geq 0.80$) were distinguished. A significance level of $\alpha = .05$ was set for all tests. However, memory functions were compared between groups on multiple variables (different aspects of memory), which results in α -error accumulation. Interpretation of results was therefore also very much based on effect sizes. Furthermore, the number of participants with impairments in each of the functions assessed was determined. This was achieved by classifying the participants' test scores on the basis of a commonly accepted categorization of ability levels (Lezak, Howieson, & Loring, 2004). Test scores lower than the "low-average" values (i.e., percentile ≤ 10) were individually classified as impaired. The percentiles of patients' test scores were calculated on the basis of test scores of a control sample ($n = 96$) with comparable characteristics with regard to age, gender, and intellectual functions. Data analysis was performed using SPSS 20 for Windows.

Results

Attention performance of participants

MANOVA indicated a significant difference of medium size in attention performance between groups (Wilk's $\lambda = 0.759$, $F(10,186) = 2.75$, $p = .003$, $\eta^2 = .129$). Significant group differences of medium size were found on all measures of attention, including tonic alertness ($F(2,97) = 6.43$, $p = .002$, $\eta^2 = .117$), phasic alertness ($F(2,97) = 5.10$, $p = .008$, $\eta^2 = .095$), selective attention ($F(2,97) = 5.37$, $p = .006$, $\eta^2 = .100$), vigilance ($F(2,97) = 3.20$, $p = .045$, $\eta^2 = .062$), and inhibition ($F(2,97) = 4.82$, $p = .010$, $\eta^2 = .090$). Post-hoc analysis revealed a significant decreased performance of patients with ADHD not-treated with MPH when compared to healthy individuals in all measures of attention, that is, tonic alertness ($p = .005$, $d = 0.73$), phasic alertness ($p = .017$, $d = 0.59$), selective attention ($p = .006$, $d = 0.76$), vigilance ($p = .047$, $d = 0.70$), and inhibition ($p = .012$, $d = 0.75$). All differences were of medium size. Patients with ADHD treated with MPH did not differ significantly from healthy individuals in all measures, as also indicated

by negligible to small effects (tonic alertness: $p = .865$, $d = 0.16$; phasic alertness: $p = .969$, $d = 0.06$; selective attention: $p = .403$, $d = 0.34$; vigilance: $p = .356$, $d = 0.38$; inhibition: $p = .669$, $d = 0.22$). The comparison of patient groups revealed that patients on medication showed a significantly increased performance of medium size in tonic alertness ($p = .030$, $d = 0.61$) and phasic alertness ($p = .043$, $d = 0.54$), whereas small non-significant differences were found on the remaining measures (selective attention: $p = .208$, $d = 0.46$; vigilance: $p = .626$, $d = 0.28$; inhibition: $p = .136$, $d = 0.47$). Table 1 presents participants' test scores as well the proportion of individuals with impairments in each of the attentional functions assessed.

Memory performance of participants

MANOVA indicated a significant difference of large size in memory functions between groups (Wilk's $\lambda = 0.425$, $F(26,176) = 3.61$, $p < .001$, $\eta^2 = .348$). Significant group differences were found on measures of short term memory ($F(2,100) = 4.76$; $p = .011$; $\eta^2 = .087$), retrospective memory (immediate word recognition: $F(2,100) = 4.01$; $p = .021$, $\eta^2 = .074$; immediate story recall: $F(2,100) = 12.90$; $p < .001$; $\eta^2 = .205$; delayed story recall: $F(2,100) = 8.14$; $p < .001$; $\eta^2 = .140$), and prospective memory (general performance: $F(2,100) = 12.67$; $p < .001$; $\eta^2 = .202$; planning: $F(2,100) = 15.51$; $p < .001$; $\eta^2 = .237$). Effects were of medium to large size. Group means, post-hoc pairwise comparisons, as well the proportion of individuals with impairments in each of the memory functions are presented in Table 2. Patients with ADHD not-treated with MPH showed a significantly decreased performance as compared to control participants in short-term memory ($p = .047$), immediate word recognition ($p = .021$), immediate story recall ($p < .001$), delayed story recall ($p = .004$), and prospective memory (general task performance ($p < .001$) and planning ($p < .001$)). Patients with ADHD on MPH displayed a significantly poorer performance than control participants in immediate story recall ($p < .001$), delayed story recall ($p = .003$), as well as both general task performance ($p < .001$) and planning ($p = .019$) of the prospective memory task. A comparison of patient groups revealed that patients on MPH performed significantly better regarding short-term memory ($p = .023$) and planning as assessed in the prospective memory task ($p = .048$) than patients off MPH. Table 3 presents effect sizes of pair-wise group comparisons (Cohen's d). However, negligible to small non-significant effects were found on the remaining measures of memory functions, including working memory ($F(2,100) = 0.36$; $p = .697$; $\eta^2 = .007$), delayed

Table 2. Memory performance ($M \pm SD$) of healthy individuals, adults with ADHD not-treated with MPH (ADHD Off-MPH), and adults with ADHD treated with MPH (ADHD On-MPH).

	Healthy individuals		Adults with ADHD			
			Off-MPH		On-MPH	
	$M \pm SD$	% with impairment ^a	$M \pm SD$	% with impairment ^a	$M \pm SD$	% with impairment ^a
Short-term memory						
Digit span forward (score)	7.9 \pm 1.9	11.1	6.9 \pm 1.7 ^b	22.2	8.1 \pm 1.7 ^c	6.5
Working memory						
Digit span backward (score)	6.6 \pm 1.9	11.1	6.5 \pm 2.0	13.9	6.3 \pm 1.6	9.7
Retrospective memory						
Immediate						
Word recognition (% recognized)	84.6 \pm 9.8	2.8	77.1 \pm 13.4 ^b	27.8	81.2 \pm 9.8	6.5
Story recall (sum score)	30.8 \pm 5.9	11.1	24.1 \pm 7.2 ^b	58.3	24.0 \pm 6.2 ^b	58.1
Delayed						
Word recognition (% recognized)	72.7 \pm 11.9	5.6	68.7 \pm 10.4	13.9	72.7 \pm 11.5	3.2
Story recall (sum score)	26.6 \pm 6.9	16.7	20.8 \pm 7.9 ^b	50.0	20.3 \pm 6.8 ^b	41.9
Retention (in %)	86.2 \pm 11.6	13.9	90.4 \pm 12.7	8.3	89.7 \pm 10.6	3.2
Source memory						
Source discrimination (% classified)	78.1 \pm 14.8	5.6	69.2 \pm 15.8	27.8	73.6 \pm 15.8	19.4
Prospective memory						
General performance (switching score)	11.3 \pm 6.6	19.4	6.1 \pm 3.9 ^b	52.8	6.2 \pm 3.5 ^b	61.3
Planning (score)	19.6 \pm 5.1	8.3	11.7 \pm 5.8 ^b	52.8	15.4 \pm 7.0 ^{b, c}	41.9
Recall (% correctly recalled)	88.4 \pm 15.9	8.3	86.5 \pm 22.0	19.4	91.4 \pm 12.4	3.2
Initiation (% of participants initiated)	0.53 \pm 0.51	–	0.47 \pm 0.51	–	0.61 \pm 0.50	–
Execution (% executed)	70.2 \pm 24.4	22.2	55.6 \pm 25.7	41.7	63.8 \pm 27.6	25.8

^aImpaired on a specific test if scored within the lowest 10% of scores of control participants ($n = 96$); ^b $p < .05$ when compared to healthy individuals; ^c $p < .05$ when compared to adults with ADHD Off-MPH.

Table 3. Effect sizes (Cohen's d) of group differences between healthy individuals, adults with ADHD not-treated with MPH (ADHD Off-MPH), and adults with ADHD treated with MPH (ADHD On-MPH).

	Healthy individuals vs. ADHD Off-MPH	Healthy individuals vs. ADHD On-MPH	ADHD Off-MPH vs. ADHD On-MPH
Short-term memory			
Digit span forward (score)	0.56	0.11	0.71
Working memory			
Digit span backward (score)	0.05	0.17	0.11
Retrospective memory			
Immediate			
Word recognition (% recognized)	0.64	0.35	0.35
Story recall (sum score)	1.02	1.13	0.02
Delayed			
Word recognition (% recognized)	0.36	0.00	0.37
Story recall (sum score)	0.78	0.92	0.07
Retention (in %)	0.35	0.31	0.06
Source memory			
Source discrimination (% classified)	0.59	0.30	0.28
Prospective memory			
General performance (switching)	0.96	0.95	0.03
Planning (score)	1.45	0.69	0.58
Recall (% correctly recalled)	0.10	0.10	0.27
Initiation (% of participants)	0.12	0.16	0.28
Execution (% executed)	0.58	0.25	0.31

word recognition ($F(2,100) = 1.47$; $p = .235$; $\eta^2 = .029$), source memory ($F(2,100) = 2.97$; $p = .056$; $\eta^2 = .056$), and prospective memory (i.e., recall: $F(2,100) = 0.64$; $p = .527$; $\eta^2 = .013$; initiation: $\chi^2(2) = 1.333$; $p = .513$; execution: $F(2,100) = 2.88$; $p = .061$; $\eta^2 = .054$; Table 2 and 3).

Discussion

The results of the present study emphasize the severity of memory impairments of adults with ADHD. Non-medicated patients with ADHD were found to have

large impairments on multiple aspects of memory which exceeded their impairments of attention in severity (impairments of attention were of medium size). The severity of memory impairments of adults with ADHD were also stressed in previous studies on neuropsychological functions of patients with ADHD (Altgassen, Kretschmer et al., 2014; Muir-Broaddus et al., 2002; Seidman et al., 1998) and can presumably be explained by the high demand of these memory functions on executive control. Contrary to our expectations, however, intact abilities of adults with ADHD were found in working memory. This appears surprising in the light

of the relatively robust findings indicating working memory deficits in ADHD as reported in meta-analyses on both children (Willcutt et al., 2005) and adults with ADHD (Alderson, Kasper, Hudec, & Patros, 2013; Schoechlin & Engel, 2005). Considering the large variety of paradigms used to assess working memory, it is also worth noting that there are studies available showing working memory deficits of adults with ADHD on the same task (Digit Span Backward) as used in the present study (Barkley, Murphy, & Kwasnik, 1996; Murphy, Barkley, & Bush, 2001). Furthermore, neuroimaging studies stressed the importance of lateral prefrontal brain regions for intact working memory in healthy adults (Cabeza & Nyberg, 2000) and also demonstrated a link between decreased working memory performance of adults with ADHD and decreased activation in these brain areas (Cubillo & Rubia, 2010). However, even though working memory deficits seem to be very prominent among adults with ADHD, it has been noted that these deficits are not universal (Alderson et al., 2013) and are thus neither necessary nor sufficient to cause ADHD (Willcutt et al., 2005) but should rather be seen as an important component of the complex neuropsychology of ADHD.

Comparing memory performance between adults with ADHD treated and not-treated with MPH, it was found that individual tailored and clinical appropriate doses of MPH improved memory performance of patients, that is, short-term memory, word recognition, source memory and prospective memory. However, adults with ADHD treated with MPH still showed considerable memory impairments when compared to a normal level of functioning, as it was revealed by large impairments in story recall and prospective memory. This is in agreement with findings of previous studies exploring effects of MPH on cognition in patients with ADHD, showing that MPH improves cognition of adults with ADHD, but does not necessarily normalize their level of performance (O. Tucha, Mecklinger et al., 2006; L. Tucha et al., 2011). Beneficial effects of stimulant medication on memory functions have also been observed in children with ADHD (e.g., Bedard et al., 2004; Rhodes et al., 2005); however, there are also clear indications that drug treatment does not necessarily normalize memory functioning of children with ADHD (Gualtieri & Johnson, 2008). The importance of a treatment of these impairments is underlined by findings showing the adverse consequences of cognitive impairments on the patients' daily life. For example, a recently published study demonstrated that adults with ADHD are aware of multiple cognitive deficits and perceive large impairments in various situations of daily life requiring cognitive functions (Fuermaier et al., 2014).

These experienced impairments do not only refer to situations associated with attention and executive functions, but also to situations requiring retrospective and prospective memory. Further improvement of memory functions of adults with ADHD on MPH might be achieved by combining the pharmacological intervention with psychosocial intervention strategies (i.e., cognitive-behavioral therapy [CBT]). Psychosocial intervention programs (such as CBT) were shown to effectively improve symptoms and executive skills of adults with ADHD (Solanto, Marks, Mitchell, Wasserstein, & Kofman, 2008; Solanto et al., 2010; Vidal-Estrada et al., 2012). A combination of both pharmacological and behavioral treatments is therefore suggested and widely regarded as the gold standard for the treatment of adults with ADHD (Rostain & Ramsay, 2006; Vidal-Estrada et al., 2012; S. B. Wigal, 2009).

Furthermore, implications can be drawn with regard to the sensitivity of neuropsychological tests in measuring effects of MPH treatment on cognition in adults with ADHD. An exploration of the size of differences (effect sizes) between patients on and off MPH indicates that the improvements were considerably larger on measures of attention than on measures of memory. This was demonstrated by performance differences on measures of attention which were up to medium size, whereas no meaningful changes were found in story recall and only small effects in word recognition. With regard to prospective memory, a difference between patient groups of medium size was only revealed by the planning task, supporting the notion that in particular measures related to attention/executive functions are sensitive to the effects of MPH on cognition of patients with ADHD. This notion is also supported by findings of previous research showing that pharmacological treatment with MPH resulted in substantial improvements of attention and planning skills of adults with ADHD (Coghill et al., 2013; Tucha, Prell, et al., 2006; Turner et al., 2005). It still remains unsolved why considerably smaller effects were found on measures of memory as compared to measures of attention/executive functions. As a possible explanation, it can be speculated that treatment with MPH improves basic cognitive functions, such as attentional functioning. The pharmacological induced improvements of these basic functions are, of course, also beneficial for various other functions that rely on these more basic functions, such as memory operations. The finding that the observed impact on memory functioning was considerably smaller might indicate that adults with ADHD could benefit from instructions and trainings focusing on how to effectively apply their heightened cognitive abilities. On the basis of the present data, it can be

concluded that a routine neuropsychological assessment of adults with ADHD is sensitive in showing the efficiency of MPH treatment in the majority of patients, with tests of attention and executive functions appearing more suited than memory tests.

Nevertheless, the value of the present results is limited since reliable conclusions on the effects of MPH are difficult to draw due to the constraints associated with a between-subject design as performed in this study. Even though the two patient groups (on and off MPH) were similar with regard to a range of characteristics (e.g., age, gender, intellectual functions and ADHD symptom severity), other characteristics differed between groups such as the distribution of ADHD subtype, comorbidity, or pharmacological treatment with antidepressant medication. Furthermore, it must be noted that self-reported symptom-severity of patients treated with MPH may not have been reliably assessed as they may have over- or underestimate their symptoms when not being treated, depending on for how long they have been on MPH. The observed differences in memory functioning attributed to pharmacological treatment could therefore also be caused by other factors. With regard to the effects of antidepressant medication, an explorative analysis of the present data did neither reveal a significant difference in measures of attention nor in measures of memory between patients treated and not-treated with antidepressant medication (data not shown). However, sample size of patients treated with antidepressant medication was small and does therefore not allow a reliable analysis. The approach of the present study, however, had also an advantage over the application of a repeated measure design by avoiding practice or carry-over effects occurring when participants are assessed repeatedly.

In conclusion, the present study is the first to provide evidence about the beneficial effects of MPH treatment on a range of memory functions of adults with ADHD. The findings reported, however, need to be replicated in future studies by applying more controlled study designs, that is, a repeated measure, placebo-controlled, cross-over design. Further evidence for the effectiveness for stimulant drug treatment could be derived from neuroimaging studies. In this respect, functional neuroimaging studies revealed an association between decreased brain activation in fronto-striatal and fronto-cerebellar areas of patients with ADHD and decreased performance in tasks assessing cognitive control (Durstun & Konrad, 2007; Valera et al., 2005). Therefore, It would be desirable if treatment studies would be combined with the application of neuroimaging techniques in order to explore the association between behavioral changes (i.e., improved

memory functions) and changes of brain activation, particularly in regions in which abnormal activation patterns have been found in patients with ADHD (Cubillo, Halari, Smith, Taylor, & Rubia, 2009; Cubillo & Rubia, 2010).

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